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(54) Title: METHODS AND COMPOSITIONS FOR TREATING ALLERGIC RHINITIS AND OTHER DISORDERS USING DESCAR-
BOETHOXYLORATADINE

(57) Abstract

Methods are disclosed utilizing DCL, a metabolic derivative of loratadine, for the treatment of allergic rhinitis, and other disorders, while avoiding the concomitant liability of adverse side-effects associated with other non-sedating antihistamines.

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METHODS AND COMPOSITIONS FOR TREATING ALLERGIC RHINITIS
AND OTHER DISORDERS USING DESCARBOETHOXYLORATADINE

1. BACKGROUND OF THE INVENTION

5 The methods of the present invention comprise administering a therapeutically effective amount of a metabolic derivative of loratadine. Chemically, this derivative is 8-chloro-6,11-dihydro-11-(4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine and known as
10 descarboethoxyloratadine (DCL). This compound is specifically described in Quercia, et al. Hosp. Formul., 28: 137-53 (1993) and U.S. Patent No. 4,659,716.

 Loratadine is an antagonist of the H-1 histamine receptor protein. The histamine receptors H-1 and H-2 are
15 two well-identified forms. The H-1 receptors are those that mediate the response antagonized by conventional antihistamines. H-1 receptors are present, for example, in the ileum, the skin, and the bronchial smooth muscle of man and other mammals.

20 Loratadine binds preferentially to peripheral rather than to central H-1 receptors. Quercia et al., Hosp. Formul. 28: 137-53 (1993). Loratadine has been shown to be a more potent inhibitor of serotonin-induced bronchospasm in guinea pigs than terfenadine. Id. at 137-38. Its anti-allergenic
25 activity in animal models was shown to be comparable to that of terfenadine and astemizole. Id. at 138. However, using standard animal model testing, on a milligram by milligram basis, loratadine was shown to be four times more potent than terfenadine in the inhibition of allergic bronchospasm. Id.
30 Moreover, loratadine's antihistaminic activity was demonstrated in humans by evaluation of the drug's ability to suppress wheal formation. Id. Clinical trials of efficacy indicated that loratadine is an effective H-1 antagonist. See Clissold et al., Drugs 37: 42-57 (1989).

35 Through H-2 receptor-mediated responses, histamine stimulates gastric acid secretion in mammals and the chronotropic effect in isolated mammalian atria. Loratadine has no effect on histamine-induced gastric acid secretion.

nor does it alter the chronotropic effect of histamine on atria. Thus, loratadine has no apparent effect on the H-2 histamine receptor.

Loratadine is well absorbed but is extensively
5 metabolized. Hilbert, et al., J. Clin. Pharmacol. 27: 694-98 (1987). The main metabolite, DCL, which has been identified, is reported to be pharmacologically active. Clissold, Drugs 37: 42-57 (1989). It is also reported as having antihistaminic activity in U.S. Patent No. 4,659,716. This
10 patent recommends an oral dosage range of 5 to 100 mg/day and preferably 10 to 20 mg/day.

Loratadine's efficacy in treating seasonal allergic rhinitis is comparable to that of terfenadine. Quercia et al., Hosp. Formul. 28: 137, 141 (1993). Loratadine also has
15 a more rapid onset of action than astemizole. Id.

Clissold et al., Drugs 37: 42, 50-54 (1989) describes studies showing loratadine as effective for use in seasonal and perennial rhinitis, colds (with pseudoephedrine), and chronic urticaria. It has also been suggested that
20 loratadine would be useful for the treatment of allergic asthma. Temple et al. Prostaglandins 35:549-554 (1988).

Loratadine may also be useful for the treatment of motion sickness and vertigo. Some antihistamines have been found to be effective for the prophylaxis and treatment of
25 motion sickness. See Wood, Drugs, 17: 471-79 (1979). Some antihistamines have also proven useful for treating vestibular disturbances, such as Meniere's disease, and in other types of vertigo. See Cohen et al., Archives of Neurology, 27: 129-35 (1972).

30 In addition, loratadine may be useful in the treatment of diabetic retinopathy and other small vessel disorders associated with diabetes mellitus. In tests on rats with streptozocin-induced diabetes, treatment by antihistamines prevented the activation of retinal histamine receptors which
35 have been implicated in the development of diabetic retinopathy. The use of antihistamines to treat retinopathy

and small vessel disorders associated with diabetes mellitus is disclosed in U.S. Patent No. 5,019,591.

It has also been suggested that loratadine, in combination with non-steroidal antiinflammatory agents or other non-narcotic analgesics, would be useful for the treatment of cough, cold, cold-like and/or flu symptoms and the discomfort, pain, headache, fever, and general malaise associated therewith. Such compositions used in the methods of treating the above-described symptoms may optionally include one or more other active components including a decongestant (such as pseudoephedrine), a cough suppressant/antitussive (such as dextromethorphan) or an expectorant (such as guaifenesin).

Many antihistamines cause adverse side-effects. These adverse side-effects include, but are not limited to, sedation, gastrointestinal distress, dry mouth, constipation or diarrhea. Loratadine has been found to cause relatively less sedation as compared with other antihistamines. Moreover, the incidence of fatigue, headache, and nausea was similar to those observed for terfenadine. See Quercia et al., Hosp. Formul. 28: 137,142 (1993).

Furthermore, compounds within the class of non-sedating antihistamines, including loratadine, astemizole, and terfenadine, have been known to cause other severe adverse electrophysiologic side-effects. These adverse side-effects are associated with a prolonged QT interval and include but are not limited to ventricular fibrillation and cardiac arrhythmias, such as ventricular tachyarrhythmias or torsades de pointes. Knowles, Canadian Journal Hosp. Pharm., 45: 33,37 (1992); Craft, British Medical Journal, 292: 660 (1986); Simons et al., Lancet, 2: 624 (1988); and Unknown, Side Effects of Drugs Annual, 12: 142 and 14: 135.

Quercia et al., Hosp. Formul. 28: 137, 142 (1993) noted that serious cardiovascular adverse side-effects, including torsades de pointes and other ventricular arrhythmias, were reported in "healthy" patients who received terfenadine concurrently with either ketoconazole or erythromycin.

Quercia et al., also states that arrhythmias have also been reported with the concomitant administration of astemizole and erythromycin or erythromycin plus ketoconazole. Thus, he cautions against using loratadine concurrently with
5 ketoconazole, itraconazole, and macrolides, such as erythromycin.

Additionally, it is also known that ketoconazole and/or erythromycin interfere with cytochrome P450, and thereby inhibit the metabolism of non-sedative antihistamines such as
10 terfenadine and astemizole. Because of the interference with the metabolism of loratadine, there exists a greater potential for adverse interaction between loratadine or other non-sedating antihistamines and drugs known to inhibit cytochrome P450, such as but not limited to ketoconazole,
15 itraconazole, and erythromycin.

In Brandes et al., Cancer Res. (52) 3796-3800 (1992), Brandes showed that the propensity of drugs to promote tumor growth in vivo correlated with potency to inhibit concanavalin A stimulation of lymphocyte mitogenesis. In
20 Brandes et al., J. Nat'l Cancer Inst., 86:(10) 771-775 (1994), Brandes assessed loratadine in an in vitro assay to predict enhancement of in vivo tumor growth. He found that loratadine and astemizole were associated with growth of both melanoma and fibrosarcoma tumors. The dose for loratadine in
25 this study was 10 mg/day.

None of the above references teach or enable the methods of the present invention comprising administering DCL to a human while avoiding adverse side-effects associated with the administration of other non-sedating antihistamines; nor do
30 the references alone or in combination suggest these methods. Thus, it would be particularly desirable to find methods of treatment with the advantages of known non-sedating antihistamines which would not have the aforementioned disadvantages.

35

2. SUMMARY OF THE INVENTION

It has now been discovered that DCL is an effective, non-sedating antihistamine which is useful in treating allergic rhinitis in a human, while avoiding adverse side-effects normally associated with the administration of other compounds within the class of non-sedating antihistamines such as loratadine, astemizole, and terfenadine. Such adverse side-effects include, but are not limited to, cardiac arrhythmias, cardiac conduction disturbances, fatigue, headache, gastrointestinal distress, appetite stimulation, weight gain, dry mouth, and constipation or diarrhea.

Furthermore, DCL is useful for treating allergic rhinitis while avoiding tumor promotion associated with loratadine and other non-sedating antihistamines. Thus, this invention also relates to novel methods of treating allergic rhinitis in a human having a higher than normal propensity for or incidence of cancer.

Furthermore, it has now also been discovered that DCL, is useful in treating allergic asthma in a human, while avoiding the adverse side-effects associated with the administration of other non-sedating antihistamines. As stated above, examples of such side-effects are appetite stimulation, weight gain, tumor promotion, cardiac arrhythmias, and cardiac conduction disturbances. Thus, this invention also relates to novel methods of treating allergic asthma in a human having a higher than normal propensity for or incidence of cancer.

In addition, DCL is useful in treating such disorders in a human as retinopathy and small vessel disorders associated with diabetes mellitus while avoiding the adverse side-effects associated with administration of other non-sedating antihistamines and while avoiding tumor promotion associated with the administration of loratadine and other non-sedating antihistamines. Thus, this invention also relates to novel methods of treating retinopathy and small vessel disorders associated with diabetes mellitus, in a human having a higher than normal propensity for or incidence of cancer.

It has also been discovered that DCL, in combination with non-steroidal antiinflammatory agents or other non-narcotic analgesics, is useful for the treatment of cough, cold, cold-like and/or flu symptoms and the discomfort, pain, 5 headache, fever, and general malaise associated therewith in a human, while avoiding the adverse side-effects associated with the administration of other non-sedating antihistamines. The use of such pharmaceutical compositions, containing DCL, and non-narcotic analgesics or non-steroidal antiinflammatory 10 agents such as aspirin, acetaminophen or ibuprofen, may optionally include one or more other active components including a decongestant (such as pseudoephedrine), a cough suppressant/antitussive (such as dextromethorphan) or an expectorant (such as guaifenesin).

15 The present invention also involves the use of the above-described compositions to treat the above-described conditions while avoiding tumor promotion associated with loratadine and other non-sedating antihistamines. Thus, the present invention also relates to the use of these 20 compositions to treat such conditions in a human having a higher than normal propensity for or incidence of cancer.

The present invention also relates to a method of avoiding interaction between DCL and a drug that inhibits cytochrome P450 including but not limited to ketoconazole, 25 itraconazole, erythromycin, and others known by those skilled in the art, while treating allergic rhinitis, allergic asthma, diabetic retinopathy and other small vessel disorders due to diabetes.

This invention is also directed to a method of avoiding 30 interaction between DCL and a drug that inhibits cytochrome P450 including but not limited to ketoconazole, itraconazole, erythromycin, and others known to those skilled in the art, while treating cough, cold, cold-like and/or flu symptoms and the discomfort, headache, pain, fever and general malaise 35 associated therewith, in a human, which comprises administering a composition to said human, said composition comprising DCL and a non-steroidal antiinflammatory agent or

non-narcotic analgesic. The aforementioned compositions may optionally contain one or more other active components including a decongestant, cough suppressant/antitussive, or expectorant.

5 It has also been discovered that DCL is useful in treating other allergic disorders related to its activity as an antihistamine, including but not limited to, urticaria and symptomatic dermatographism, in a human, while avoiding the adverse side-effects associated with the administration of
10 other non-sedating antihistamines and/or while avoiding tumor promotion associated with the administration of loratadine and other non-sedating antihistamines. Thus, this invention also relates to novel methods of treating allergic disorders, including but not limited to, urticaria and symptomatic
15 dermatographism in a human having a higher than normal propensity for or incidence of cancer. The present invention also relates to methods of avoiding interaction between loratadine or other non-sedating antihistamines and a drug that inhibits cytochrome P450 including but not limited to
20 ketoconazole, itraconazole, and erythromycin, and others known by those skilled in the art, while treating allergic disorders, including but not limited to, urticaria and symptomatic dermatographism wherein said human is administered DCL.

25

3. DETAILED DESCRIPTION OF THE INVENTION

The present invention encompasses a method of treating allergic rhinitis in a human while avoiding the concomitant liability of adverse side-effects associated with the
30 administration of non-sedating antihistamines, which comprises administering to said human a therapeutically effective amount of DCL or a pharmaceutically acceptable salt thereof.

The present invention further encompasses a method of
35 treating allergic asthma in a human while avoiding the concomitant liability of adverse side-effects associated with the administration of non-sedating antihistamines, which

comprises administering to said human a therapeutically effective amount of DCL or a pharmaceutically acceptable salt thereof.

Also included in the present invention is a method of
5 treating retinopathy or other small vessel diseases associated with diabetes mellitus in a human while avoiding the concomitant liability of adverse side-effects associated with the administration of non-sedating antihistamines, which comprises administering to said human a therapeutically
10 effective amount of DCL or a pharmaceutically acceptable salt thereof.

The present invention further encompasses a method of treating cough, cold, cold-like, and/or flu symptoms and the discomfort, headache, pain, fever, and general malaise
15 associated therewith, in a human, while avoiding the concomitant liability of adverse side-effects associated with the administration of non-sedating antihistamines, which comprises administering to said human a composition, said composition comprising (i) a therapeutically effective amount
20 of DCL or a pharmaceutically acceptable salt thereof and (ii) a therapeutically effective amount of at least one non-steroidal antiinflammatory agent or non-narcotic analgesic such as acetylsalicylic acid, acetaminophen, ibuprofen, ketoprofen, and naproxen, or a pharmaceutically acceptable
25 salt thereof.

Additionally, the present invention encompasses a method of treating cough, cold, cold-like, and/or flu symptoms and the discomfort, headache, pain, fever, and general malaise associated therewith, in a human, while avoiding the
30 concomitant liability of adverse side-effects associated with the administration of non-sedating antihistamines, which comprises administering to said human a composition, said composition comprising (i) a therapeutically effective amount of DCL or pharmaceutically acceptable salt thereof, and (ii)
35 a therapeutically effective amount of a decongestant such as pseudoephedrine or a pharmaceutically acceptable salt thereof.

It has been found that DCL is five to seven times less active in tumor promotion than loratadine. Thus, the present invention further encompasses a method of treating allergic rhinitis in a human while avoiding the concomitant liability of tumor promotion associated with the administration of loratadine and other non-sedating antihistamines, which comprises administering to said human a therapeutically effective amount of DCL or a pharmaceutically acceptable salt thereof.

10 A further aspect of the present invention includes a method of treating allergic asthma in a human while avoiding the concomitant liability of tumor promotion associated with the administration of loratadine and other non-sedating antihistamines, which comprises administering to said human a
15 therapeutically effective amount of DCL or a pharmaceutically acceptable salt thereof.

The present invention further encompasses a method of treating retinopathy or other small vessel diseases associated with diabetes mellitus in a human while avoiding
20 the concomitant liability of tumor promotion associated with the administration of loratadine and other non-sedating antihistamines, which comprises administering to said human a therapeutically effective amount of DCL or a pharmaceutically acceptable salt thereof.

25 Because DCL is much less active than loratadine at promoting tumors, a further aspect of this invention is a method of treating allergic rhinitis in a human wherein said human has a higher than normal propensity for or incidence of cancer, which comprises administering to said human a
30 therapeutically effective amount of DCL or a pharmaceutically acceptable salt thereof.

The present invention further encompasses a method of treating allergic asthma in a human wherein said human has a higher than normal propensity for or incidence of cancer,
35 which comprises administering to said human a therapeutically effective amount of DCL or a pharmaceutically acceptable salt thereof.

Also included in the present invention is a method for treating retinopathy or other small vessel diseases associated with diabetes mellitus in a human wherein said human has a higher than normal propensity for or incidence of cancer, which comprises administering to said human a therapeutically effective amount of DCL or a pharmaceutically acceptable salt thereof.

Furthermore, the present invention also includes a method of treating cough, cold, cold-like, and/or and flu symptoms and the discomfort, headache, pain, fever and general malaise associated therewith, in a human, wherein said human has a higher than normal propensity for or incidence of cancer, which comprises administering to said human a composition, said composition comprising (i) a therapeutically effective amount of DCL or a pharmaceutically acceptable salt thereof, and (ii) a therapeutically effective amount of a non-steroidal antiinflammatory agent or non-narcotic analgesic such as acetylsalicylic acid, acetaminophen, ibuprofen, ketoprofen, and naproxen, or a pharmaceutically acceptable salt thereof.

Moreover, the present invention further encompasses a method of treating cough, cold, cold-like and/or flu symptoms and the discomfort, headache, pain, fever and general malaise associated therewith, in a human, wherein said human has a higher than normal propensity for or incidence of cancer, which comprises administering to said human a composition, said composition comprising (i) a therapeutically effective amount of DCL or a pharmaceutically acceptable salt thereof, and (ii) a therapeutically effective amount of a decongestant such as pseudoephedrine or a pharmaceutically acceptable salt thereof.

It has also been found that when DCL is concurrently administered with a drug that inhibits cytochrome P450 including but not limited to ketoconazole, itraconazole, erythromycin and others known by those skilled in the art, the interaction between said DCL and said drug is decreased

in comparison to the concurrent administration of loratadine or other non-sedating antihistamines with said drug.

Therefore, this invention also encompasses a method of avoiding interaction between DCL and a drug that inhibits
5 cytochrome P450 including but not limited to ketoconazole, itraconazole, erythromycin and others known by those skilled in the art, while treating allergic rhinitis in a human, wherein said human is administered DCL or a pharmaceutically acceptable salt thereof.

10 Moreover, this invention also encompasses a method of avoiding interaction between loratadine or other non-sedating antihistamines and a drug that inhibits cytochrome P450 including but not limited to ketoconazole, itraconazole, erythromycin and others known by those skilled in the art,
15 while treating allergic asthma in a human, wherein said human is administered DCL or a pharmaceutically acceptable salt thereof.

This invention also encompasses a method of avoiding interaction between DCL and a drug that inhibits cytochrome
20 P450 including but not limited to ketoconazole, itraconazole, erythromycin and others known by those skilled in the art, while treating retinopathy or other small vessel diseases associated with diabetes mellitus in a human, wherein said human is administered DCL or a pharmaceutically acceptable
25 salt thereof.

Also encompassed by the present invention is a method of avoiding interaction between DCL and a drug that inhibits cytochrome P450 including but not limited to ketoconazole, itraconazole, erythromycin and others known by those skilled
30 in the art, while treating cough, cold, cold-like, and/or flu symptoms and the discomfort, headache, pain, fever and general malaise associated therewith, in a human, which comprises administering to said human a composition, said composition comprising (i) a therapeutically effective amount
35 of DCL or a pharmaceutically acceptable salt thereof, and (ii) a therapeutically effective amount of a non-steroidal antiinflammatory agent or non-narcotic analgesic, such as

acetylsalicylic acid, acetaminophen, ibuprofen, ketoprofen, and naproxen, or a pharmaceutically acceptable salt thereof.

A further aspect of the invention is a method of avoiding interaction between DCL and a drug that inhibits cytochrome P450 including but not limited to ketoconazole, itraconazole, erythromycin and others known by those skilled in the art, while treating cough, cold, cold-like, and/or flu symptoms and the discomfort, headache, pain, fever and general malaise associated therewith, in a human, which comprises administering to said human a composition, said composition comprising (i) a therapeutically effective amount of DCL or a pharmaceutically acceptable salt thereof; and (ii) a therapeutically effective amount of a decongestant such as pseudoephedrine or a pharmaceutically acceptable salt thereof.

A further aspect of this invention includes a method of treating urticaria in a human while avoiding the concomitant liability of adverse side-effects associated with the administration of non-sedating antihistamines, comprising administering to said human a therapeutically effective amount of DCL or a pharmaceutically acceptable salt thereof.

Furthermore, the present invention includes a method of treating symptomatic dermographism in a human while avoiding the concomitant liability of adverse side-effects associated with the administration of non-sedating antihistamines, comprising administering to said human a therapeutically effective amount of DCL or a pharmaceutically acceptable salt thereof.

It has also now been found that DCL is at least about twenty times more potent at the histamine receptor when compared to loratadine. Thus, the dosage range by the modes of administration described herein and for use in the methods of the present invention, are about 0.1 to less than about 10 mg per day. This is significantly lower than what has been recommended for other non-sedating antihistamines, including loratadine which has a recommended oral dose of 5 to 100 mg per day. However, due to the significantly less side-

effects, DCL can be given in doses higher than those suggested for loratadine thereby offering an improved therapeutic range than loratadine.

Loratadine and other non-sedating antihistamines have antihistaminic activity and provide therapy and a reduction of symptoms for a variety of conditions and disorders related to allergic rhinitis and other allergic disorders, diabetes mellitus and other conditions; however, such drugs, while offering the expectation of efficacy, causes adverse side-effects. Utilizing DCL results in clearer dose-related definitions of efficacy, diminished adverse side-effects, and accordingly, an improved therapeutic index. It is, therefore, more desirable to use DCL than to use loratadine itself or other non-sedating antihistamines.

The term "adverse effects" includes, but is not limited to cardiac arrhythmias, cardiac conduction disturbances, appetite stimulation, weight gain, sedation, gastrointestinal distress, headache, dry mouth, constipation, and diarrhea. The term "cardiac arrhythmias" includes, but is not limited to ventricular tachyarrhythmias, torsades de pointes, and ventricular fibrillation.

The phrase "therapeutically effective amount" means that amount of DCL which provides a therapeutic benefit in the treatment or management of allergic rhinitis and other allergic disorders such as urticaria, symptomatic dermatographism, allergic asthma, retinopathy or other small vessel disorders associated with diabetes mellitus, and the symptoms associated with allergic rhinitis such as cough, cold, cold-like, and/or flu symptoms including, but not limited to, sneezing, rhinorrhea, lacrimation, and dermal irritation.

The term "allergic asthma" is defined as a disorder characterized by increased responsiveness of the trachea and bronchi to various stimuli which results in symptoms which include wheezing, cough, and dyspnea.

The term "diabetic retinopathy" or "retinopathy associated with diabetes mellitus" is that disorder caused by

increased permeability of the capillaries in the eye which leads to hemorrhages and edema in the eye and can lead to blindness. The term "small vessel disorders associated with diabetes mellitus" includes, but is not limited to, diabetic 5 retinopathy and peripheral vascular disease.

The magnitude of a prophylactic or therapeutic dose of DCL in the acute or chronic management of disease will vary with the severity of the condition to be treated and the route of administration. The dose, and perhaps the dose 10 frequency, will also vary according to the age, body weight, and response of the individual patient. In general, the total daily dose range, for the conditions described herein, is from about 0.1 mg to less than about 10 mg administered in single or divided doses orally, topically, transdermally, or 15 locally by inhalation. For example, a preferred oral daily dose range should be from about 0.1 mg to about 5 mg. A more preferred oral dose is about 0.2 mg to about 1 mg.

It is further recommended that children, patients aged over 65 years, and those with impaired renal or hepatic 20 function initially receive low doses, and that they then be titrated based on individual response(s) or blood level(s). It may be necessary to use dosages outside these ranges in some cases as will be apparent to those skilled in the art. Further, it is noted that the clinician or treating physician 25 will know how and when to interrupt, adjust, or terminate therapy in conjunction with individual patient response.

The term "therapeutically effective amount of DCL or a pharmaceutically acceptable salt thereof" is encompassed by the above-described dosage amounts. In addition, the terms 30 "said composition comprising (i) a therapeutically effective amount of DCL or a pharmaceutically acceptable salt thereof, and (ii) a therapeutically effective amount of at least one non-steroidal antiinflammatory agent or non-narcotic or a pharmaceutically acceptable salt thereof"; and 35 "said composition comprising (i) a therapeutically effective amount of DCL or a pharmaceutically acceptable salt thereof, and (ii) a therapeutically effective amount of a decongestant

such as pseudoephedrine or a pharmaceutically acceptable salt thereof" are also encompassed by the above-described dosage amounts and dose frequency schedule.

Any suitable route of administration may be employed for
5 providing the patient with an effective dosage of DCL according to the methods of the present invention. For example, oral, rectal, parenteral, transdermal, subcutaneous, intramuscular, and like forms of administration may be employed. Dosage forms include tablets, troches,
10 dispersions, suspensions, solutions, capsules, patches, and the like.

The pharmaceutical compositions used in the methods of the present invention comprise DCL, the metabolic derivative of loratadine, as active ingredient, or a pharmaceutically
15 acceptable salt thereof, and may also contain a pharmaceutically acceptable carrier, and optionally, other therapeutic ingredients.

The term "pharmaceutically acceptable salt" refers to a salt prepared from pharmaceutically acceptable non-toxic
20 acids or bases including inorganic acids or bases or organic acids or bases. Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic, sulfuric, and phosphoric. Appropriate organic acids may be selected, for example, from aliphatic, aromatic, carboxylic and sulfonic
25 classes of organic acids, examples of which are formic, acetic, propionic, succinic, glycolic, glucuronic, maleic, furoic, glutamic, benzoic, anthranilic, salicylic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, pantothenic, benzenesulfonic, stearic,
30 sulfanilic, algenic, and galacturonic. Examples of such inorganic bases include metallic salts made from aluminum, calcium, lithium, magnesium, potassium, sodium, and zinc. Appropriate organic bases may be selected, for example, from N,N-dibenzylethylenediamine, chloroprocaine, choline,
35 diethanolamine, ethylenediamine, meglumine (N-methylglucamine), lysine and procaine.

The compositions for use in the methods of the present invention include compositions such as suspensions, solutions and elixirs; aerosols; or carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents, and the like, in the case of oral solid preparations (such as powders, capsules, and tablets), with the oral solid preparations being preferred over the oral liquid preparations. The most preferred oral solid preparations are tablets.

10 Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are employed. If desired, tablets may be coated by standard aqueous or nonaqueous techniques.

15 In addition to the common dosage forms set out above, the compound for use in the methods of the present invention may also be administered by controlled release means and/or delivery devices such as those described in U.S. Patent Nos. 3,845,770; 3,916,899; 3,536,809; 3,598,123; and 4,008,719, 20 the disclosures of which are hereby incorporated by reference.

Pharmaceutical compositions for use in the methods of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets, or 25 tablets, or aerosol sprays, each containing a predetermined amount of the active ingredient, as a powder or granules, or as a solution or a suspension in an aqueous liquid, a non-aqueous liquid, an oil-in-water emulsion, or a water-in-oil liquid emulsion. Such compositions may be prepared by any of 30 the methods of pharmacy, but all methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid 35 carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired presentation.

For example, a tablet may be prepared by compression or molding, optionally, with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form
5 such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Molded tablets may be made by molding, in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. Desirably, each tablet contains from about
10 0.1 mg to less than about 10 mg of the active ingredient, and each cachet or capsule contains from about 0.1 mg to about less than 10 mg of the active ingredient, i.e., DCL.

The invention is further defined by reference to the following examples describing in detail the preparation of
15 the compound and the compositions used in the methods of the present invention, as well as their utility. It will be apparent to those skilled in the art that many modifications, both to materials and methods, may be practiced which are within the scope of this invention.

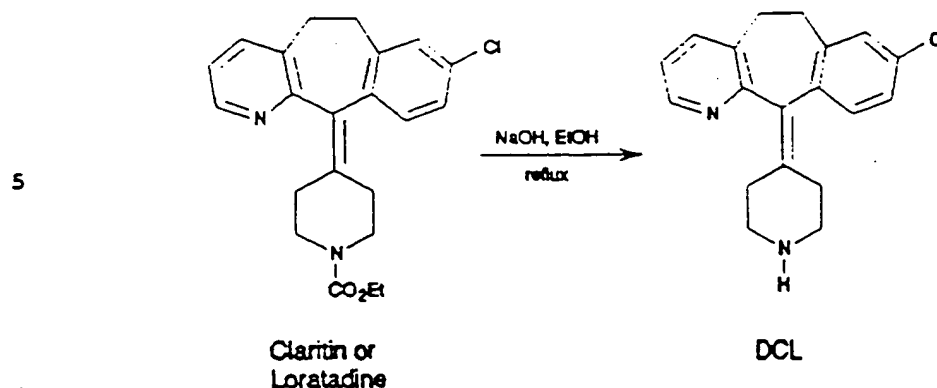
20

4. EXAMPLES

4.1 Example 1: Preparation of loratadine and its metabolites

25 Loratadine can be synthesized by methods disclosed in U.S. patent No. 4,282,233. The metabolites are prepared similarly, by reaction steps conventional in the art, as described in U.S. patent No. 4,659,716 which is incorporated here by reference in its entirety. One common method of
30 preparing DCL is to reflux loratadine in the presence of sodium hydroxide and ethanol as depicted below.

35



Extraction of Commercially Available Claritin Tablets (600x10 mg):

Tablets of loratadine, were diluted with water and chloroform. The mixture was stirred, then filtered through celite, rinsed with chloroform until the filtrate contained no loratadine. The separated aqueous layer was extracted with chloroform twice. The combined organic layer was washed with water, brine and dried over sodium sulfate. The solvent was evaporated to give pure loratadine as a white solid.

Saponification of loratadine:

Loratadine (4.0 g) was added to a solution of sodium hydroxide (5.9 g) in 280 mL of absolute ethanol and the mixture was stirred at reflux for four days. The mixture was cooled and concentrated to remove ethanol. The residue was diluted with water and aqueous layer was extracted with methylene chloride five times. The combined organic layer was washed with water, brine and dried over sodium sulfate. The solvent was evaporated to give 2.82 g (87%) of pure loratadine derivative (or metabolite) as a pale-tan solid.

4.2 Example 2

Antihistaminic Activity

The antihistaminic activity of loratadine and DCL were compared in isolated strips of guinea pig ileum contracted with histamine. This preparation is generally accepted by

those skilled in the art as predicative of its efficacy as a peripheral histamine H-1 receptor.

Methods:

5 Experiments were performed on pieces of ileum taken from male guinea pigs (Hartley strain, 419-560 grams; Elm Hill Breeding Laboratories, Chelmsford, MA). The tissues were suspended in tissue chambers containing 40 ml of Tyrode's solution aerated with 95% oxygen and 5% carbon dioxide at 35°
10 C. The Tyrode's solution contained (in mM) 137 NaCl, 2.7 KCl, 2.2 CaCl₂, 0.025 MgCl₂, 0.4 NaHPO₄, 11.9 NaHCO₃, and 5.5 glucose. Contractions in response to histamine were recorded with isotonic transducers (Model 357, Harvard Apparatus Company, South Natick, MA) using an ink-writing polygraph
15 (Model 7, Grass Instrument Company, Quincy, MA). A tension of one gram was maintained on all tissues at all times.

In each experiment three or four pieces of ileum were removed from a single animal, suspended in individual tissue chambers and allowed to equilibrate with the bathing solution
20 for one hour before the administration of any drugs. In four initial experiments in which tissues were exposed to histamine at concentrations of 1×10^{-7} , 1×10^{-6} and 1×10^{-5} mol/l, histamine at 1×10^{-6} mol/l produced strong contractions on the linear portion of the log-concentration-effect curve and this
25 concentration of histamine was chosen for use in all further experiments.

For determining the antihistaminic effects of loratadine and DCL, tissues were exposed briefly (about 15 seconds) to 1×10^{-6} mol/l of histamine at intervals of 15 minutes. After
30 two successive exposures to histamine produced contractions of approximately the same magnitude, loratadine or DCL, at final concentrations that varied three- or ten-fold, was added to all but one of the tissue chambers, the untreated tissue serving as a control for the treated tissues. After
35 each exposure of drug-treated tissues to histamine, the fluid in the tissue chamber was replaced with fluid free of histamine but containing the same drug at the same

concentration. The histamine challenges were made at 5, 20, 35, 50, 65, 80, 95, 110 and 125 minutes of exposure to the drug or at comparable times in the control tissues.

Subsequent analyses of the results from each experiment 5 involved (i) normalization of the data from each tissue for differences in inherent contractility by expressing all contractions as a percent of the last predug contraction, (ii) normalization of the data for possible time-related changes in contractility by expressing the contractions 10 recorded during drug-exposure as a percent of the corresponding value for the untreated tissue, and finally (iii) calculation of the drug-related percent reduction of each contraction.

The resultant sets of data for drug concentration and 15 corresponding percent reduction in histamine-response were then used to estimate for each experiment the concentration of drug that would have produced a 50 percent reduction in the histamine response, the IC_{50} . This was done by fitting straight lines to the data using the method of least squares 20 and calculating the IC_{50} from the equation of the line. The mean \pm standard error of the values for the experiments on each drug were calculated, and differences between the drugs was examined using the Kruskal Wallis 1-way analysis of variance by ranks.

25 A summary of the results are shown in the following two tables. The percentages of reduction of histamine-induced contractions of the isolated guinea pig ileum produced by exposure for 125 minutes to various concentrations of each drug are set forth below:

30

35

TABLE 1 - Reduction of Histamine-induced
Guinea Pig Ileum Contractions (Percent)

5	<u>Drug</u>	<u>Expt No.</u>	<u>Concentration of drug (mol/l)</u>					
			3×10^{-10}	1×10^{-9}	3×10^{-9}	1×10^{-8}	3×10^{-8}	1×10^{-7}
	Loratadine	1	-	19.05	-	13.33	-	88.57
10		2	-	-	-	28.32	54.42	98.66
		3	-	-	-	39.64	44.68	93.38
		4	-	-	-	55.86	45.83	86.46
15	DCL	1	11.93	73.12				
		2	38.91	38.81	56.71			
		3	40.00	62.69	76.21			
20		4	35.43	44.13	76.43			
25								
30								
35								

The methods described by Dini et al., which is hereby incorporated by reference herein (Agents and Actions, 33:181-184, 1991), were used for these binding studies. Guinea pig cerebella membranes were incubated with 0.5 nM 3H-pyrilamine for 10 min at 25°C. Following incubation, the assays were rapidly filtered under vacuum through GF/B glass fiber filters (Whatman) and washed several times with ice-cold buffer using a Brandel Cell Harvester. Bound radioactivity was determined with a liquid scintillation counter (LS 6000, Beckman) using a liquid scintillation cocktail (Formula 989, DuPont NEN).

IC₅₀ values were determined for compounds tested and pyrilamine at the H-1 histamine receptor:

15 Table 3 - Inhibition of Pyrilamine Binding at H-1 Receptor

H-1 receptor		
Compound	IC ₅₀ (nM)	(nH)
Loratadine	721	(1.55)
DCL	51.1	(1.12)
20 Pyrilamine	1.4	(0.98)

As shown above, DCL was found to have a 14 fold greater affinity than loratadine for histamine H-1 receptors. These results are consistent with the findings demonstrating a higher potency of DCL over loratadine for inhibition of histamine-induced contractions of guinea pig ileum.

These studies confirm that DCL has a higher potency for histamine receptors than loratadine.

30

4.4 Example 4

Tumor Promoting Activity

Inhibition of lymphocyte mitogenesis was used to screen the potencies of loratadine and DCL as tumor promoting agents.

35

Mitogenesis studies:

Fresh spleen cells (5×10^5) obtained from 5-week old BALB/c mice (Charles River, ST. Constant, PQ) were suspended in RPMI 1640 medium containing 2% fetal calf serum (Grand Island Biological Co., Grand Island, NY) seeded into 5 replicate microwell plates (Nunc) to which concanavalin (Con) A ($2 \mu\text{g/ml}$; Sigma Chemical Co., St. Louis, MO) was added and incubated (37°C , 95% air, 5% CO_2) in the absence or presence of increasing concentrations of the test agents dissolved in saline or other vehicles. Forty-three hours after the 10 addition of Con A, $0.25 \text{ nmol } ^3\text{H-thymidine}$ (6.7 Ci/nmol ; ICN Radiopharmaceuticals, Montreal, PQ) was added to each well. After an additional 5-hour incubation, the cells were washed from the wells onto filter papers employing an automated cell sorter. The filters were placed into vials containing 5 ml 15 scintillation fluid (Readysafe; Beckman), and radioactivity incorporated into DNA at 48 hours was determined ($n = 3$). IC_{50} values for inhibition of mitogenesis were determined over wide range of concentrations (0.1 to $10 \mu\text{M}$).

20 Table 4 - Inhibition of Concanavalin A
Induced Stimulation of Lymphocytes (IC_{50})

Loratadine	$1.0 \mu\text{M}$
DCL	$5.6 \mu\text{M}$

These results indicate that DCL is 5-7 fold less active 25 than loratadine at promoting tumor growth.

4.5 Example 5

Cardiovascular Effects

The effects of DCL on cardiac potassium currents were 30 studied.

Methods:

Single ventricular myocytes of the guinea-pig and the rabbit were dissociated by enzymatic dispersion (see 35 Carmeliet, J. Pharmacol. Exper. Ther., 1992, 262, 809-817 which is incorporated herein by reference in its entirety). The single suction patch electrode, with a resistance of 2 to

5 MΩ was used for voltage clamp (Axoclamp 200A). P-clamp software (Axon Instruments) was used to generate voltage-clamp protocols and to record and analyze data. The standard solution contained in mM: NaCl 137.6, KCl 5.4, CaCl₂ 1.8, 5 MgCl₂ 0.5, HEPES 11.6 and glucose 5, and NaOH was added to pH 7.4. The intracellular solution contained KCl 120, MgCl₂ 6, CaCl₂ 0.154, Na₂ATP 5, EGTA 5, and HEPES 10, with KOH added until pH 7.2.

10 Effect on the delayed rectifying K⁺ current, (I_K) in rabbit ventricular myocytes:

The voltage clamp protocol consisted of clamps from a holding potential of -50 mV to +10 mV for a duration of 4 sec. The change in tail current was measured as a function 15 of the drug concentration. This concentration was changed between 10⁻⁷ and 10⁻⁵ M in five steps. Exposure to each concentration lasted 15 min. At the end, washout was attempted during 30 min.

20 Effect on the inward rectifier current in guinea-pig myocytes:

The inward rectifier was measured by applying ramp voltage clamps starting from -50 mV and hyperpolarizing the membrane to -120 mV at a speed of 10 mV/sec. The starting concentration was the 50% efficiency concentration, 25 determined in the preceding experiments. Higher concentrations were applied if this initial concentration was without effect.

30 Effect on I_K in guinea-pig ventricular myocytes:

Tail currents were measured following depolarizing clamps of 2 sec duration to potentials between -30 mV and +60 mV; holding potential -50mV.

The results from these studies indicate that DCL is less active than terfenadine in inhibiting the cardiac delayed 35 rectifier and thus has no potential for cardiac side-effects.

TABLE 2 - Reduction of Histamine-induced
Guinea Pig Icum Contractions (IC₅₀)

	<u>Drug</u>	<u>Expt</u>	<u>IC₅₀(M)</u>
5	Loratadine	1	1.90x10 ⁻⁸
		2	2.21x10 ⁻⁸
		3	2.10x10 ⁻⁸
10		4	1.22x10 ⁻⁸
		Mean	1.86x10 ⁻⁸
		S.E.	0.22
15	DCL	1	6.36x10 ⁻¹⁰
		2	19.2x10 ⁻¹⁰
20		3	5.26x10 ⁻¹⁰
		4	8.66x10 ⁻¹⁰
		Mean	9.75x10 ⁻¹⁰
25		S.E.	3.20

Note: There is a statistically significant drug-related difference in IC₅₀ values (P=0.0209).

30 These results indicate that DCL is approximately 20 fold more potent at the histamine receptor than loratadine.

4.3 Example 3

Receptor binding studies

35 Receptor binding studies on the binding affinities of loratadine and DCL at histamine H-1 receptors were performed.

Thus, the methods of the present invention are less toxic than methods which use other non-sedating antihistamines.

4.6 Example 6

5 Inhibition of cytochrome P450

This study is conducted to determine the extent that loratadine and DCL inhibit human cytochrome P4503A4 (CYP3A4). CYP3A4 is involved in many drug-drug interactions and quantitation of inhibition of CYP3A4 by loratadine or DCL indicates the potential of such drug-drug interactions. Inhibition is measured using the model substrate testosterone and cDNA-derived CYP3A4 in microsomes prepared from a human lymphoblastoid cell line designated h3A4v3.

15 Study Design:

The inhibition study consists of the determination of the 50% inhibitory concentration (IC_{50}) for the test substance. A single testosterone concentration (120 μ M, approximately twice the apparent K_m) and ten test substance concentrations, separated by approximately $1/2$ log, are tested in duplicate. Testosterone metabolism is assayed by the production of the 6(β)-hydroxytestosterone metabolite. This metabolite is readily quantitated via HPLC separation with absorbance detection.

25

Storage/Preparation of the test substances and addition to the incubations:

The test substances will be stored at room temperature. The test substances will be dissolved in ethanol for addition to the incubations. The solvent concentration will be constant for all concentrations of the test substance.

IC_{50} Determination:

Final test substance concentrations will be 100, 30, 10, 3, 1, 0.3, 0.1, 0.03, 0.01, 0.003 and 0 μ M. Each test concentration will be tested in duplicate incubations in accordance with the method below:

Method:

A 0.5 ml reaction mixture containing 0.7 mg/ml protein, 1.3 mM NADP⁺, 3.3 mM glucose-6-phosphate, 0.4 U/ml glucose-6-phosphate dehydrogenase, 3.3 mM magnesium chloride and 120 μ M testosterone in 100 mM potassium phosphate (pH 7.4) will be incubated at 37°C for 30 min. A known quantity of 11(β)-hydroxytestosterone will be added as an internal standard to correct for recovery during extraction. The reaction mixture will be extracted with 1 ml methylene chloride. The extract will be dried over anhydrous magnesium sulfate and evaporated under vacuum. The sample will be dissolved in methanol and injected into a 4.6 x 250 mm 5 μ C18 HPLC column and separated at 50°C with a mobile phase methanol/water at a flow rate of 1 ml per min. The retention times are approximately 6 min for the 6(β)-hydroxy, 8 min for 11(-)-hydroxy and 12 min for testosterone. The product and internal standard are detected by their absorbance at 254 nm and quantitated by correcting for the extraction efficiency using the absorbance of the 11(β)-hydroxy peak and comparing to the absorbance of a standard curve for 6(β)-hydroxytestosterone.

Data reporting:

For each test substance, the concentration of 6(β)-hydroxytestosterone metabolite in each replicate incubation is determined and the percentage inhibition relative to solvent control is calculated. The IC₅₀ is calculated by linear interpolation.

Useful pharmaceutical dosage forms for administration of the compounds used in the methods of the present invention can be illustrated as follows:

4.7. Example 7Capsules

A large number of unit capsules are prepared by filling standard two-piece hard gelatin capsules each with 0.1 to 10 milligrams of powdered active ingredient, 150 milligrams of lactose, 50 milligrams of cellulose, and 6 milligrams magnesium stearate.

4.8. Example 810 Soft Gelatin Capsules

A mixture of active ingredient in a digestible oil such as soybean oil, lecithin, cottonseed oil or olive oil is prepared and injected by means of a positive displacement pump into gelatin to form soft gelatin capsules containing 15 0.1 to 10 milligrams of the active ingredient. The capsules are washed and dried.

4.9 Example 9Tablets

20 A large number of tablets are prepared by conventional procedures so that the dosage unit was 0.1 to 10 milligrams of active ingredient, 0.2 milligrams of colloidal silicon dioxide, 5 milligrams of magnesium stearate, 275 milligrams of microcrystalline cellulose, 11 milligrams of starch and 25 98.8 milligrams of lactose. Appropriate coatings may be applied to increase palatability or delay absorption.

Various modifications of the invention in addition to those shown and described herein will be apparent to those skilled in the art from the foregoing description. Such 30 modifications are also intended to fall within the scope of the appended claims.

The foregoing disclosure includes all the information deemed essential to enable those skilled in the art to practice the claimed invention. Because the cited patents or 35 publications may provide further useful information these cited materials are hereby incorporated by reference in their entireties.

What is claimed is:

1. A method of treating allergic rhinitis in a human while avoiding the concomitant liability of adverse side-effects associated with the administration of non-sedating antihistamines, comprising administering to said human a therapeutically effective amount of DCL or a pharmaceutically acceptable salt thereof.
2. The method of claim 1 wherein said adverse side-effect is cardiac arrhythmia or tumor promotion.
3. The method of claim 1 wherein said human has a higher than normal propensity for or incidence of cancer.
4. The method of claim 1, wherein interaction between DCL and a drug that inhibits cytochrome P450 is avoided.
5. The method of claim 1 wherein the amount of DCL administered is from about 0.1 mg to less than about 10 mg per day.
6. The method of claim 5 wherein the amount of DCL administered is from about 0.1 mg to about 5 mg per day.
7. The method of claim 1 wherein the amount of said DCL or a pharmaceutically acceptable salt thereof is administered together with a pharmaceutically acceptable carrier.
8. A method of treating allergic asthma in a human while avoiding the concomitant liability of adverse side-effects associated with the administration of non-sedating antihistamines, comprising administering to said human a therapeutically effective amount of DCL or a pharmaceutically acceptable salt thereof.

9. The method of claim 8 wherein said adverse side-effect is cardiac arrhythmia or tumor promotion.

10. The method of claim 8 wherein said human has a 5 higher than normal propensity for or incidence of cancer.

11. The method of claim 8, wherein interaction between DCL and a drug that inhibits cytochrome P450 is avoided.

10 12. The method of claim 8 wherein the amount of DCL administered is from about 0.1 mg to less than about 10 mg per day.

13. The method of claim 12 wherein the amount of DCL 15 administered is from about 0.1 mg to about 5 mg per day.

14. The method of claim 8 wherein the amount of said DCL or a pharmaceutically acceptable salt thereof is administered together with a pharmaceutically acceptable 20 carrier.

15. A method for treating retinopathy or other small vessel diseases associated with diabetes mellitus in a human while avoiding the concomitant liability of adverse side- 25 effects associated with the administration of non-sedating antihistamines, comprising administering to said human a therapeutically effective amount of DCL or a pharmaceutically acceptable salt thereof.

30 16. The method of treating claim 15 wherein said adverse side-effect is cardiac arrhythmia or tumor promotion.

17. The method of claim 15 wherein said human has a higher than normal propensity for or incidence of cancer.

35

18. The method of claim 15 wherein interaction between DCL and a drug that inhibits cytochrome P450 is avoided.

19. The method of claim 15 wherein the amount of DCL administered is from about 0.1 mg to less than about 10 mg per day.

5 20. The method of claim 19 wherein the amount of DCL administered is from about 0.1 mg to about 5 mg per day.

21. The method of claim 15 wherein the amount of said DCL or a pharmaceutically acceptable salt thereof is
10 administered together with a pharmaceutically acceptable carrier.

22. A method for treating cough, cold, cold-like or flu symptoms and the discomfort, headache, pain, fever and
15 general malaise associated therewith, in a human, while avoiding the concomitant liability of adverse side-effects associated with the administration of non-sedating antihistamines, comprising administering to said human a composition, said composition comprising (i) a
20 therapeutically effective amount of DCL or a pharmaceutically acceptable salt thereof, and (ii) a therapeutically effective amount of a non-steroidal antiinflammatory agent or non-narcotic analgesic, or a pharmaceutically acceptable salt thereof.

25

23. The method of claim 22 wherein said adverse side-effect is cardiac arrhythmia or tumor promotion.

24. The method of claim 22 wherein said human has a
30 higher than normal propensity for or incidence of cancer.

25. The method of claim 22, wherein interaction between DCL and a drug that inhibits cytochrome P450 is avoided.

35 26. The method of claim 22 wherein said composition further comprises from about 0.1 mg to less than about 10 mg

of DCL and from about 25 mg to about 600 mg of said anti-inflammatory or analgesic.

27. The method of claim 22, wherein said composition further comprises a pharmaceutically acceptable carrier.

28. A method for treating cough, cold, cold-like or flu symptoms and the discomfort, headache, pain, fever and general malaise associated therewith, in a human, while avoiding the concomitant liability of adverse side-effects associated with the administration of non-sedating antihistamines, comprising administering to said human a composition, said composition comprising (i) a therapeutically effective amount of DCL or a pharmaceutically acceptable salt thereof, and (ii) a therapeutically effective amount of a decongestant or a pharmaceutically acceptable salt thereof.

29. The method of claim 28 wherein said adverse side-effect is cardiac arrhythmia or tumor promotion.

30. The method of claim 28 wherein said human has a higher than normal propensity for or incidence of cancer.

31. The method of claim 28 wherein interaction between DCL and a drug that inhibits cytochrome P450 is avoided.

32. The method of claim 28 wherein the said composition further comprises from about 0.1 mg to less than about 10 mg of said DCL and from about 5 mg to about 150 mg of said decongestant.

33. The method of claim 28, wherein said composition further comprises a pharmaceutically acceptable carrier.

35

34. A method of treating urticaria in a human while avoiding the concomitant liability of adverse side-effects

associated with the administration of non-sedating antihistamines, comprising administering to said human a therapeutically effective amount of DCL or a pharmaceutically acceptable salt thereof.

5

35. The method of claim 34 wherein said adverse side-effect is cardiac arrhythmia or tumor promotion.

36. The method of claim 34 wherein said human has a
10 higher than normal propensity for or incidence of cancer.

37. The method of claim 34, wherein interaction between DCL and a drug that inhibits cytochrome P450 is avoided.

15 38. The method of claim 34 wherein the amount of DCL administered is from about 0.1 mg to less than about 10 mg per day.

39. The method of claim 38 wherein the amount of DCL
20 administered is from about 0.1 mg to about 5 mg per day.

40. The method of claim 34 wherein the amount of said DCL or a pharmaceutically acceptably salt thereof is administered together with a pharmaceutically acceptable
25 carrier.

41. A method of treating symptomatic dermographism in a human while avoiding the concomitant liability of adverse side-effects associated with the administration of non-
30 sedating antihistamines, comprising administering to said human a therapeutically effective amount of DCL or a pharmaceutically acceptable salt thereof.

42. The method of claim 41 wherein said adverse side-
35 effect is cardiac arrhythmia or tumor promotion.

43. The method of claim 41 wherein said human has a higher than normal propensity for or incidence of cancer.

44. The method of claim 41, wherein interaction between 5 DCL and a drug that inhibits cytochrome P450 is avoided.

45. The method of claim 41 wherein the amount of DCL administered is from about 0.1 mg to less than about 10 mg per day.

10

46. The method of claim 42 wherein the amount of DCL administered is from about 0.1 mg to about 5 mg per day.

47. The method of claim 41 wherein the amount of said 15 DCL or a pharmaceutically acceptably salt thereof is administered together with a pharmaceutically acceptable carrier.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/15995

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : A61K 31/44

US CL : 514/290

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/290

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS:

SEARCH TERMS: DESCARBOETHOXYLORATADINE AND ALLERGI?

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO.A, 85/03707 (SCHERING CORPORATION) 29 August 1985, see entire document.	1-47
Y	BIOCHEMICAL PHARMACOLOGY; vol. 47, no.. 5, issued 1994, B. BERTHON et al., "In Vitro Inhibition, By Loradine and Descarboxyloratadine, of Histamine Release From Human Basophils and of Histamin Release and Intracellular Calcium Fluxex In Rat Basophilic Leukemia Cells" pages 789-794. see entire document.	1-47

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	* T	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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* O* document referring to an oral disclosure, use, exhibition or other means		
* P* document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

08 APRIL 1996

Date of mailing of the international search report

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INTERNATIONALER RECHERCHENBERICHT

ationales Aktenzeichen

PCT/EP 95/04761

A. KLASSIFIZIERUNG DES ANMELDUNGSGEGENSTANDES
IPK 6 A61K9/70 A61K31/445

Nach der internationalen Patentklassifikation (IPK) oder nach der nationalen Klassifikation und der IPK

B. RECHERCHIERTE GEBIETE

A: recherchierte Mindestprüfstoff (Klassifikationssystem und Klassifikationssymbole)
IPK 6 A61K

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Während der internationalen Recherche konsultierte elektronische Datenbank (Name der Datenbank und evtl. verwendete Suchbegriffe)

C. ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
X	US,A,4 910 205 (KOGAN ET AL.) 20.März 1990 siehe das ganze Dokument ---	1-6
A	HOSP. FORMUL., Bd. 28, Nr. 2, 1993 Seiten 137-153, XP 000566896 R.A. QUERCIA ET AL. 'Focus on loratidine: a new second-generation nonsedating H1-receptor antagonist.' ---	
A	PHARMAZIE, Bd. 49, Nr. 10, 1994 Seiten 736-739, XP 000566477 D. ZHONG ET AL. 'HPLC-determination of loratidine and its active metabolite descarboethoxyloratidine in human plasma.' -----	

☐ Weitere Veröffentlichungen sind der Fortsetzung von Feld C zu entnehmen

☒ Siehe Anhang Patentfamilie

* Besondere Kategorien von angegebenen Veröffentlichungen :

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